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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,699	02/10/2004	David Bebbington	VPI/00-130-07 DIV US	9174

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 12/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/775,699	BEBBINGTON ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01-10-05 (Prelim. Admt)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-19,24,25 and 29-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-19,24,25 and 29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-10-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's preliminary amendment of 01-10-05 is acknowledged and entered.

Claims 2-7, 20-23 and 26-28 are cancelled.

Claims 1, 8-19, 24, 25 and 29-34 are pending.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Scope of Enablement:** Claims 17-19, 24, 25, 30, 31 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of lowering blood level of glucose (or treating diabetes) by enhancing glycogen synthesis, does not reasonably provide enablement for a method of treating many diseases that are allegedly related to Aurora-2, GSK-3, Tau protein, or β-catenin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 17 recites: "A method of inhibiting Aurora-2 or GSK-3 activity in a biological sample..." which appears to include a diagnostic method.

Claim 18 depends on claim 15, and recites: "A method of inhibiting Aurora-2 activity in a patient..." which covers the treatment of various cancers such as colon and breast cancers as well as other solid tumors.

Claim 19 depends on claim 16, and recites: "A method of inhibiting Aurora-2 activity in a patient..." which covers the same treatment as recited in claim 18, but using a combination of the claimed compound and an additional agent.

Claim 24 depends on claim 15, and recites: "A method of inhibiting GSK-3 activity in a patient..." which covers the treatment of diabetes, Alzheimer's disease, CNS disorders, neurodegenerative disease, cardiomyocete hypertrophy.

Claim 25 depends on claim 16, and recites: "A method of inhibiting GSK-3 activity in a patient..." which covers the same treatment recited in claim 24, but using a combination of the claimed compound and an additional agent.

Claim 30 depends on claim 15, and recites: "A method of inhibiting the production of hyperphosphorylated Tau protein in a patient..." which covers the "halting or slowing the progression of Alzheimer's disease."

Claim 31 depends on claim 15, and recites: "A method of inhibiting the phosphorylation of β-catenin ..." which covers the treatment of schizophrenia.

Claim 34 depends on claim 15, and recites: "A method of treating diabetes, Alzheimer's disease, schizophrenia, cardiomycete hypertrophy, or reperfustion/ischemia in a patient..." which obviously covers the treatment of diseases of different etiologies and manifestation.

Thus, the scopes of claims 18, 19, 24, 25 and 34 are unduly broad. The scopes of claims 17, 30 and 31 are not so broad, but are drawn to method of diagnosis, or treatment that appear to overlap with claims 18, 19, 24, 25 and 34.

The amount of direction or guidance presented:

The specification only provides *in-vitro* data for the inhibitory activity of the claimed compounds on Aurora-2, GSK-3, Tau protein, and β-catenin. It also provides literature in trying to correlate those activities to the treatment of various diseases. However, for many diseases listed, there is no crucial evidence that the claimed compounds can treat any of them, except diabetes due to the activity of GSK-3 (glycogen synthase kinase -3). Thus, the specification does

not provide sufficient guidance for the skilled clinician to treat a variety of diseases allegedly related to Aurora-2, GSK-3, Tau protein, and β-catenin.

The state of the prior art:

Currently in the practice of medicine, there is no single agent that can treat diabetes, Alzheimer's disease, cardiomycete hypertrophy, various tumors, etc. In fact, Tacrine, a commercial drug to treat early stage of Alzheimer's disease does not lower blood glucose level. Furthermore, despite the progess in the treatment of Alzheimer's disease, presently there is no agent that can "halt" Alzheimer's disease, especially in the late stage. While the specification tries to correlate the treatment of schizophrenia with the inhibition of β-catenin, presently, schizophrenia still cannot be treated since it has no known cause. Thus, the state of the prior art does not support the treatment of many diseases as claimed herein.

The relative skill of those in the art:

Even with the advanced training, the skilled clinician would have to carry out extensive research to select an effective compound from the large Markush group of formula II. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound. Given a large Markush group of the claimed formula II, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the

instant case, the specification only describes *in-vitro* assays without indicating which compounds have been tested. However, said description alone does not adequately guide the skilled clinician in the treatment of diseases of various etiologies and manifestation. Thus, with such a limited teaching, the skilled clinician would have to carry out undue experimentation to use the claimed compounds in the methods recited in claims 17-19, 24, 25, 30, 31 and 34.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 8-19, 24, 25 and 29-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. The limitation of "prodrug" in claim 1 and wherever it appears has indefinite metes and bounds because it is not clear what constitutes the ester or amide of a prodrug, and its location on the compound of formula II.

b. Claim 1 recites variable L and its definition. However, said variable does not appear to have a relationship with formula II.

c. Claims 17 recites: "A method of inhibiting Aurora-2 or GSK-3 activity in a biological sample..." which has indefinite metes and bounds because it is not clear if a diagnostic method is intended, or an analytical bioassay is intended.

d. Claims 18 and 19, both recite: "A method of inhibiting Aurora-2 activity..." which has indefinite metes and bounds because it is not clear what diseases are being treated.

e. Claims 24 and 25, both recite: "A method of inhibiting GSK-3 activity..." which has indefinite metes and bounds because it is not clear what diseases are being treated.

f. Claim 30 recites: "A method of inhibiting the production of hyperphosphorylated Tau protein..." which has indefinite metes and bounds because it is not clear what diseases are being treated.

g. Claim 31 recites: "A method of inhibiting the phosphorylation of β-catenin ..." which has indefinite metes and bounds because it is not clear what diseases are being treated.

h. Claims 8-19, 24, 25 and 29-34 are also rejected for being (ultimately) dependent on claim 1 and carrying over the indefinite limitations.

Reference cited on PTO-892

The reference cited on PTO-892 shows state of the art only. While said reference teaches compounds of (2-(aryl or heteroaryl)-NH)-pyrimidine, it fails to teach a substituent equivalent to R^y at the 6^{th} position on the pyrimidine ring.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Tamthom N. Truong
Examiner
Art Unit 1624

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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12-6-05